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	First Named Inventor	CHOO, Yen
	Art Unit	1639
	Examiner Name	Wessendorf, T.
	Attorney Docket Number	019496-006210US

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Date	October 21, 2005	Reg. No.	37,505

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PTO/SB/17 (12-04)

Effective on 12/08/2004.

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL

For FY 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 250

Complete if Known

Application Number 09/424,482
Filing Date February 29, 2000
First Named Inventor CHOO, Yen
Examiner Name Wessendorf, T.
Art Unit 1639
Attorney Docket No. 019496-006210US

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Small Entity	Fee (\$)	Small Entity	Fee (\$)	Small Entity	Fee (\$)	
Utility	300	150	500	250	200	100	_____
Design	200	100	100	50	130	65	_____
Plant	200	100	300	150	160	80	_____
Reissue	300	150	500	250	600	300	_____
Provisional	200	100	0	0	0	0	_____

2. EXCESS CLAIM FEES

Fee Description	Small Entity	Fee (\$)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims Extra Claims Fee (\$) Fee Paid (\$) Multiple Dependent Claims Fee (\$) Fee Paid (\$)

-20 or HP = _____ x _____ = _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims Extra Claims Fee (\$) Fee Paid (\$)

-3 or HP = _____ x _____ = _____

HP = highest number of independent claims paid for, if greater than 3

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets Extra Sheets Number of each additional 50 or fraction thereof Fee (\$) Fee Paid (\$)

- 100 = _____ / 50 = _____ (round up to a whole number) x _____ = _____

4. OTHER FEE(S)

Non-English Specification, \$130 fee (no small entity discount)

Other: Filing a brief in support of an appeal

250

SUBMITTED BY

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PATENT
Attorney Docket No.: 019496-006210US
Client Ref. No. G2-US

On October 21, 2005

TOWNSEND and TOWNSEND and CREW LLP

By: [Signature]
Susan M. Johnson

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re application of:

Yen Choo et al.

Application No.: 09/424,482

Filed: February 29, 2000

For: NUCLEIC ACID BINDING POLYPEPTIDE
LIBRARY

Examiner: T. Wessendorf

Art Unit: 1639

**APPELLANTS' BRIEF UNDER
37 CFR § 41.37**

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed on August 31, 2005 for the above-referenced application, Appellants submit this Brief on Appeal.

10/24/2005 HDESTA1 00000104 201430 09424482

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TABLE OF CONTENTS

1. REAL PARTY IN INTEREST	3
2. RELATED APPEALS AND INTERFERENCES.....	3
3. STATUS OF CLAIMS	3
4. STATUS OF AMENDMENTS	3
5. SUMMARY OF CLAIMED SUBJECT MATTER	3
6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL	4
7. ARGUMENT	4
8. CONCLUSION.....	12
9. CLAIM APPENDIX.....	13
10. EVIDENCE APPENDIX.....	24
11. RELATED PROCEEDING APPENDIX.....	25

1. REAL PARTY IN INTEREST

Gendaq Ltd., a wholly owned subsidiary of Sangamo Biosciences, Inc.

2. RELATED APPEALS AND INTERFERENCES

This is the second appeal of the present case. The first appeal was settled after submission of the appeal brief, and the case allowed (see notice of allowance mailed January 15, 2004). However, the signed information disclosure statement attached to the notice of allowance struck numerous references. Appellants filed a request for continued examination (RCE) to have the information disclosure statement considered in full. The RCE filing resulted in several substantive rejections in part over references addressed in the previous appeal leading to the present appeal.

3. STATUS OF CLAIMS

Claims 1, 2, 6, 7 and 27-34 are pending. Claims 3-5 and 8-26 are canceled. The claims are listed in Appendix A.

4. STATUS OF AMENDMENTS

The most recent amendment was made in a response filed April 27, 2005, which has been entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present claims are directed to libraries of zinc finger proteins in which positions 2 and 6 of adjacent zinc fingers are at least partially randomized. Claim 1 specifies a zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger. Amino acids within each zinc finger protein are assigned numbers from -1 to +9 in accordance with convention whereby position +1 is the first residue of an alpha helix (specification at p. 7, lines 5-9). Each polypeptide member of the library is at least partially randomized such that randomization extends to cover at least position 6 of one finger and position 2 of an adjacent finger. Because these residues contact the same base pair of a target, it is advantageous they be varied together (specification at p. 9, lines 5-9). Co-randomization of these residues results in zinc finger proteins with additional binding specificities compared to zinc finger proteins obtained by previous methods (compare specification at p. 2, lines 12-27 (discussing prior art) and p. 36, lines 20-29, discussing results obtained with the presently claimed invention). The additional specificities result because of binding interactions between adjacent fingers, and randomization of residues from both fingers is needed to

encompass the full range of binding specificities. Claim 1 also specifies a set of amino acid residues to which randomization is restricted (specification at p. 11, lines 7-10). Randomization with a restricted set of residues occupying position 2 is advantageous because it increases the number of productive combinations with amino acids occupying position 6 in the adjacent finger (specification at p. 10, line 20 to p. 11, line 2), and allows more randomization of other positions without exceeding constraints on overall library size.

Independent claim 30 is similar to claim 1 except that it specifies a set of amino acids residues to which randomization at position 6 is restricted (see specification at p. 11, Table 1).

Claim 29, which depends from claim 1, specifies sets of amino acids to which randomization is restricted for both positions 2 and 6.

Claims 27 and 33 specify an embodiment in which randomization occurs at positions -1, 1, 2, 3, 5 and 6 of a first finger and -1, 1, 2 and 3 of a second finger. Claims 28 and 34 specify another embodiment in which randomization occurs at positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second zinc finger (specification at p. 9, lines 16-22).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

6.1 Whether claims 1-2, 6-7 and 27-34 comply with the written description requirement of 35 USC 112, first paragraph.

6.2 Whether claims 6 and 32 are definite under 35 USC 112, second paragraph.

6.3 Whether claims 1-2, 6-7 and 27-34 would have been obvious under 35 USC 103 over Greisman et al., Science 275, 657-561 (1997) [Greisman] in view of Choo et al. Current Opinion in Biotechnology 6, 431-436 (1995) [Choo].

7. ARGUMENT

7.1. Claims 1-2, 6-7 and 27-34 Comply with 35 USC 112, First Paragraph

The final office action mailed July 25, 2005 (final office action) alleges that claims 1 and 30 lack written description in that the Markush group of amino acids occupying position 2 or 6 of a zinc finger (i.e., D, A R Q, H, K, S, N and R, Q, V, A, E, K, N, T respectively) are disclosed only in the context of co-randomization of each of the remaining positions (-1, 1, 3, 4, 5) and with randomization at these positions restricted to the Markush groups for these positions recited in claim

Initially, it is noted that this basis of rejection, applied to all the claims, is clearly inapplicable to claim 7, which, as admitted by the Examiner, specifies particular amino acid residues for all of positions -1, 1, 2, 3, 5 and 6. Thus, in claim 7, randomization at each of positions -1, 1, 2, 3, 5 and 6 is confined to a Markush group as the Examiner is proposing would be acceptable for the other claims.

The specification also provides written description for the other claims. The written description requirement does not require in haec verba antecedence in the originally filed application. *Staehelin v. Secher*, 24 USPQ2d 1111, 1117 (Fed. Cir. 1991). All that is required is that the description convey with reasonable clarity to person of skill in the art that the inventor was in possession of whatever is now claimed. *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Here, it is respectfully submitted that the specification does reasonably evidence appellants' possession of a zinc finger library, randomized at positions 6 and 2 of adjacent first and second fingers, in which randomization at position 2 is confined to D, A, R, Q, H, K, S, and N or randomization at position 6 is confined to R, Q, V, A, E, K, N, and T, without necessarily requiring randomization at any other position or confining randomization at each of the remaining positions -1, 1, 2, 3, 5 and 6 to the Markush group of amino acids specified for that position in claim 7. For example, the specification states at page 11, lines 13-14: "It is not necessary for each finger to be randomized at each of the positions [-1, 1, 2, 3, 5, 6] given in Table 1. In addition, the specification provides a table of amino acids "*preferably selected*" to appear at each position (p. 11, lines 3-14, emphasis supplied). The table lists D, A, R, Q, H, K, S, and N for position 2 and R, Q, V, A, E, K, N, and T for position 6. By using the term "preferably selected," the specification conveys that position 2 is preferably occupied by D, A, R, Q, H, K, S, and N, but can less preferably be occupied by other amino acids. Likewise position 6 is preferably occupied by R, Q, V, A, E, K, N, T, but can also be occupied by other amino acids. Similar preferred groups of amino acids are provided for other positions. The table does not state that if one position is occupied by a preferred group of amino acids, then every other position must also be occupied by its preferred group of amino acids. To the contrary, as noted above, the specification states that it is not necessary for each

listed position to be randomized (p. 11, lines 13-14). In other words, the preferences for amino acids at the various positions listed in the table do not have to apply simultaneously or not at all. Accordingly, the specification reasonably evidences appellants' possession of zinc finger proteins in which randomization at position 2 is confined to D, A, R, Q, H, K, S, and N or randomization at position 6 is confined to R, Q, V, A, E, K, N, and T, without necessarily requiring that each other position in Table 1 is randomized at all, or if it is randomized, that randomization is necessarily confined to the preferred Markush group of amino acids for the position listed in Table 1.

7.2 Claims 6 and 32 are Definite Under 35 USC 112, Second Paragraph

Claims 6 and 32 are alleged to be unclear as to how the limitation of selecting the randomized positions from positions -1, 1, 2, 3, and 6 applies to the respective base claims (final office action at pp. 3-4). The Examiner asks, if position -1 is selected how does it extend to cover position 6?

In response, claims 1 and 30 specify that at least positions 2 and 6 are randomized, implying that other positions may, but need, not be randomized. Claims 6 and 32 specify that the randomized positions are selected from positions -1, 1, 2, 3, 5, and 6. These claims add the additional limitation relative to claims 1 and 30 that if additional positions beyond 2 and 6 are randomized, these positions are other positions from the recited group. To answer the Examiner's question, if position -1 is randomized, the randomization can extend to position 6, by position 6 being randomized as well.

The second paragraph of 35 U.S.C. § 112 requires only that persons skilled in the art are reasonably apprised of the scope of the claim. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 USPQ 633, 641 (Fed. Cir. 1985). Here, persons skilled in the art are reasonably apprised of the scope of claims 6 and 32 as indicating that if additional positions beyond 2 and 6 are randomized then the positions are selected from the group recited in claims 1 and 30. No other plausible interpretation of these claims has been proposed by the Examiner. Accordingly, it is respectfully submitted that the Examiner has not established a case of indefiniteness, and the rejection should be reversed.

7.3. Claims 1-2, 6-7 and 27-34 Not Obvious Under 35 USC 103 Over Greisman in

View of Choo

7.3.1. The Cited Art

Greisman discusses an iterative strategy for making zinc finger proteins, which involves randomizing and selecting one finger at a time. The method is iterative in that finger(s) that have previously been selected provide context for selection of another finger. In brief, in a first step, a zinc finger protein comprising one randomized finger and two constant fingers is selected. In a second step, a second zinc finger protein comprising one randomized finger, one previously selected finger, and one constant finger is selected. In a third step, a zinc finger protein comprising one randomized finger and two previously selected fingers is selected. The iterative method of selection has the advantage that new fingers are selected in a relevant structural context.

Choo discusses a different strategy for making zinc finger proteins, in which the individual fingers of the zinc finger protein are randomized and selected independently of each other. After selection of individual fingers, random combinations of the fingers are selected *en bloc* (paragraph bridging pp. 433-434). This *en bloc* selection procedure is said to partly circumvent problems of position and context.

7.3.2. Undisclosed Elements

The prior art references when combined must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Here, the cited references do not teach or suggest the groups of amino acids recited in independent claim 1 and claim 30 to which partial randomization of amino acids is restricted (D, A, R, Q, H, K, S, and N, in claim 1 and R, Q, V, A, E, K, N, and T in claim 30). As noted above, Greisman randomizes a single finger at a time and therefore fails to disclose a library in which positions 6 and 2 in adjacent fingers are simultaneously randomized. Moreover, in randomizing a single finger at a time, Greisman teaches to randomize in such a manner as to allow any of sixteen amino acids at each position (footnote 15 of Greisman). The four omitted amino acids are omitted as part of a strategy to avoid stop codons

(id.). Choo does not explicitly disclose whether he restricted randomization to certain codons. However, reference to his earlier work cited in the Choo paper (see reference 7¹ of the Choo paper cited at p. 4321 first column, fourth paragraph of the Choo paper) shows that he, like Greisman, restricted randomization to sixteen amino acids. A patent by Choo, US 6,007,988 (of record) also omitted four amino acids and explained that the reason was to avoid stop codons ("T in the first base position is omitted in order to avoid stop codons, but this has the *unfortunate* effect that the codons for Trp, Phe, Tyr and Cys are not represented" (at col. 12, 24-27, emphasis supplied)).

The view that omitting the above amino acids was "unfortunate" teaches away from performing randomization with additional amino acids omitted. Therefore, the cited references neither individually or in combination teach or suggest the claimed groups of amino acids to which randomization should be restricted.

7.3.3. Lack of Motivation to Combine

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 123 USPQ 349 (CCPA 1959). Here, the Examiner takes the position that it would have been obvious to combine Choo's *en bloc* selection with Greisman's iterative method for the benefit of the advantage provided by Choo (office action of April 27, 2005 at p. 5). However, the Examiner appears to overlook that the advantage of *en bloc* selection in Choo's method arises because of the previous context-independent selection of individual fingers. In such a method, there is no context to lose by random assortment of the fingers and reselection *en bloc*. By contrast, Greisman has devised an elaborate iterative method which serves to select each successive finger in the context of previously selected finger(s). Random recombination of fingers followed by further selection *en bloc* would lose the benefits of context provided by the iterative method. Therefore, the proposed incorporation of Choo into Greisman's methods is inconsistent with the principle of operation of Greisman's method.

¹ Choo et al., Proc. Natl. Acad. Sci. USA 91, 11163-11167 (1994) (#78 on IDS) at p. 11164, second column third paragraph.

7.3.4. Rebuttal of Examiner's Comments

The Examiner disagrees with appellants' position that the limitation of randomization to defined groups of amino acids in claims 1 or 30 distinguishes the cited art on the basis that the claims, as construed by the Examiner, are not so limited (final office action at p. 6). Specifically, the Examiner takes the view that the use of the term "comprising" in the phrase "zinc finger comprising amino acid positions -1 to + 9" leaves the subsequent recital of "wherein the randomization of amino acid residues at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S and N" open to amino acids beyond those listed in the group. An analogous allegation is raised with respect to independent claim 30.

In response, the Examiner's position arises from a confusion between two distinct elements of the claim. The term "comprising" modifies the amino acid positions forming a zinc finger of a zinc finger protein. In other words, a zinc finger can and usually does have more positions than those (-1 to + 9) enumerated in the claim. The term "comprising" does not however modify a distinct element of the claim, namely the set of amino acids to which randomization is restricted at one particular position (position 2 in claim 1, and position 6 in claim 30). Here, the recital that "randomization of amino acid residues at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S and N" means exactly what it says, that randomization is limited to the recited group of amino acids and no others. The same is true regarding the analogous recital in claim 30. Thus, these claims are distinguished from the cited references based on the sets of amino acids to which randomization is limited.

The Examiner also appears to disagree with appellants' position because the independent claims, although requiring randomization of both positions 2 and 6, specify the set of amino acids to which randomization is restricted for only one of these positions. The Examiner quotes appellants' previous remarks that restriction of partial randomization to preferred groups of amino acids is advantageous, both because it increase the representation of productive combinations of amino acids at these positions and because it allows greater variation at other positions without exceeding constraints on overall library size (final office action at p. 5).

In response, even if the Examiner were correct that an advantage can only be achieved by restricting randomization to limited sets of amino acids at both positions 2 and 6, "[n]othing in the patent statute requires than an invention be superior to the prior art to be patentable." *Ryco Inc. v. Ag. Bag Corp.*, 8 USPQ2d 1323, 1328 (Fed. Cir. 1988). In fact, although restricting the sets of amino acids at both positions 2 and 6 is optimal, restriction of the set of amino acids at one position and not the other still allows the above noted advantages to be achieved in part. For example, if randomization of position 2 is restricted to the set of amino acids at position 2, and position 6 is randomized without restriction then, relative to the situation in which both positions are fully randomized, there is still a higher representation of productive combinations of amino acids at these positions and still the possibility of greater variation at other positions without exceeding constraints on overall library size.

This basis for disagreement with appellants' position is irrelevant to claims 7 and 29, both of which do limit randomization of both positions 2 and 6 to preferred sets of amino acids.

The Examiner also disagrees with appellants' position on the basis that simply picking a combination of positions 2 and 6 to randomize is prima facie obvious. The Examiner cites *Chore-Time Equipment, Inc. v. Cumberland Corp.* 218 USPQ 673 (Fed. Cir. 1983) apparently for the proposition that more than synergism is required for patentability.

In response, appellants first note that the Examiner is not addressing the claims, as currently drafted, in that the claims do not merely require combined randomization of positions 2 and 6 but also restriction of amino acids to a defined set at one or both of these positions. Second, *Chore-Time Equipment* does not hold that more than synergism is required for patentability. The case arose in relevant part because a lower court held the claimed invention obvious based on lack of synergy relative to the cited art. The Federal Circuit found that the showing of synergy was not required for patentability stating:

A requirement that an invention reflect "synergism" or achieve a "synergistic result," before it may be held patentable appears nowhere in the statute 35 U.S.C. The test of obviousness under 35 U.S.C. §103,

as the statute makes plain, is whether the invention as a whole would have been obvious at the time it was made to one of ordinary skill in the art. References to synergism as a patentability requirement are, therefore unnecessary and confusing.

218 USPQ 673, 667.

Chore-Time Equipment thus holds that synergism is not necessary for patentability.

Such is consistent with appellants' position under *Ryco Inc. v. Ag. Bag Corp.*, 8 USPQ2d 1323, 1328 (Fed. Cir. 1988) discussed above.

7.3.5 Additional Grounds of Patentability of Dependent Claims

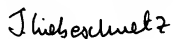
Claim 29 is directed to an embodiment of the invention in which randomization at positions 6 and 2 of adjacent fingers is restricted to defined sets of amino acids. Randomization with restricted sets of amino acids at both positions 2 and 6 can be advantageous because the amino acids occupying these positions can bind to the same nucleotide of a target site (specification at p. 9, lines 5-9), and the simultaneous restriction of amino acids increases the representation of productive combinations of amino acids for binding to that site (specification at p. 10, line 20 to p. 11, line 2), as well as allowing greater randomization at other positions in the zinc fingers without exceeding constraints of library size. Neither reference discloses or suggests randomization of positions 2 and 6 with randomization at both positions limited to sets of amino acids as defined in claim 29.

Claims 27, 28, 33 and 34 are directed to embodiments which effectively allow randomization of zinc fingers in units of about one and a half fingers at a time (see specification at p. 9, lines 10-22). A unit size of approximately one and half fingers allows co-randomization at positions 2 and 6, thereby generating binding specificities resulting from interactions between amino acids occupying these positions, but leaves flexibility in randomizing other desired positions without exceeding constraints of library size. Units of approximately one and a half fingers can be recombined after randomization as described in the specification at p. 9, lines 11-15. The cited art does not disclose or suggest randomization at positions -1, 1, 2, 3, 5 and 6 of a first finger and positions -1, 1, 2 and 3 of a second finger (as recited in claim 27 or claim 33) or positions 3, 5, and 6 of a first finger and -1, 1, 2 and 3 of a second finger as recited in claim 28 or 34.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,



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9. CLAIM APPENDIX

Claim 1. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to +9 with position 1 representing the first amino acid of an alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover at least positions 6 and 2 of adjacent first and second fingers, respectively, wherein the randomisation of amino acid residues at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S, and N.

Claim 2. A library according to claim 1 wherein each polypeptide comprises between three and six zinc fingers.

Claims 3-5. (canceled)

Claim 6. A library according to claim 1, wherein the randomised positions are selected from positions -1, 1, 2, 3, 5 and 6.

Claim 7. A library according to claim 1, wherein the randomization of amino acid residues is restricted such that the following amino acids appear at the given positions:

Position	Amino Acids
-1	R, Q, H, N, D, A, T
1	S, R, K, N
2	D, A, R, Q, H, K, S, N
3	H, N, S, T, V, A, D
5	I, T, K
6	R, Q, V, A, E, K, N, T

Claims 8-26. (canceled)

Claim 27. A library according to claim 1 wherein positions -1, 1, 2, 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

Claim 28. A library according to claim 1 wherein positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

Claim 29. A library according to claim 1, wherein the randomization of amino acid residues at position 2 is restricted to amino acids selected from the group consisting of D, A, R, Q, H, K, S, and N, and at position 6 is restricted to amino acids selected from the group consisting of R, Q, V, A, E, K, N, and T.

Claim 30. A zinc finger polypeptide library in which each polypeptide comprises more than one zinc finger comprising amino acid positions -1 to +9 with position 1 representing the first amino acid of an alpha-helix and wherein each polypeptide has been at least partially randomised such that the randomisation extends to cover at least positions 6 and 2 of adjacent first and second fingers, respectively, wherein the randomisation of amino acid at position 6 is restricted to amino acids selected from the group consisting of R, Q, V, A, E, K, N, and T.

Claim 31. A library according to claim 30 wherein each polypeptide comprises between three and six zinc fingers.

Claim 32. A library according to claim 30, wherein the randomised positions are selected from positions -1, 1, 2, 3, 5 and 6.

Claim 33. A library according to claim 31 wherein positions -1, 1, 2, 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

Claim 34. A library according to claim 31 wherein positions 3, 5 and 6 of a first zinc finger and -1, 1, 2 and 3 of a second finger are randomized.

10. Evidence Appendix

Choo et al., Proc. Natl. Acad. Sci. USA 91, 11163-11167 (1994) (#78 on IDS) (considered by Examiner January 25, 2004)

Choo, US 6,007,988 (#2 on IDS) (considered by Examiner January 25, 2004)

11. Related Proceedings Appendix

A previous appeal was filed September 16, 2003 in the present case. Because the case was allowed before being transferred to the Board, the case did not result in any Board or Court opinion.